Elvitegravir (EVG)

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Formulations

Tablet: Elvitegravir is available only in fixed-dose combination (FDC) tablets.

FDC Tablets

- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

When using FDC tablets, refer to other sections of the Appendix A. Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/c/FTC/TAF)

Child (Weighing ≥14 to <25 kg)

- Limited data are available on the dose of Genvoya in children with weight ≥14 kg to <25 kg. A study is being conducted to assess the safety and efficacy of an investigational low-dose tablet with EVG 90 mg/cobicistat (COBI) 90 mg/FTC 120 mg/TAF 6 mg.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily with food in antiretroviral therapy (ART)–naive or treatment-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/c/FTC/TDF)

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily with food in ART-naive or treatment-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

Selected Adverse Events

Genvoya- and Stribild-Associated Adverse Events

- Nausea
- Diarrhea
- Fatigue
- Headache

TAF-Specific Adverse Events

- Increased levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol
- Glomerular and proximal renal tubular dysfunction (less common when compared to TDF)

TDF-Specific Adverse Events

- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density
- Flatulence

COBI-Specific Adverse Events

- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine

Special Instructions

- Administer both Genvoya and Stribild with food.
- Genvoya and Stribild should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.
- When using Genvoya or Stribild, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before initiating FTC, TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued. In patients with HBV, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF.
- For information on crushing and cutting tablets, see the Information on Crushing and Liquid Drug Formulations table from Toronto General Hospital.

Metabolism/Elimination

- EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- EVG is available only in combination with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the COBI, TDF, and TAF sections for further details on the metabolism of these drugs.

EVG Dosing in Patients with Hepatic Impairment

- Stribild and Genvoya **should not be used** in patients with severe hepatic impairment.

EVG Dosing in Patients with Renal Impairment

- Stribild **should not be initiated** in patients with estimated CrCl <70 mL/min, and it should be discontinued in patients with estimated CrCl <50 mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya is **not recommended** in patients with estimated CrCl 15 to <30 mL/min or in patients with estimated CrCl <15 mL/min who are not receiving chronic hemodialysis.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Absorption:* Elvitegravir (EVG) plasma concentrations are lower with concurrent administration of divalent cations due to the formation of complexes in the gastrointestinal tract and not due to changes in gastric pH. Therefore, Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.[1]
- *Metabolism:* Stribild and Genvoya contain EVG and cobicistat (COBI). COBI itself does not have antiretroviral (ARV) activity, but it is a cytochrome P450 (CYP) 3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir (RTV).[2] EVG is metabolized predominantly by CYP3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative metabolism pathways. EVG is a moderate inducer of CYP2C9. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. In addition, COBI inhibits the adenosine triphosphate–dependent transporters, P-glycoprotein and the breast cancer resistance protein, and the organic anion-transporting (OAT) polypeptides OATP1B1 and OATP1B3. See the Cobicistat section for a more detailed summary of drug interactions. Multiple drug interactions are possible when using both EVG and COBI. Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain RTV because of the similar effects of COBI and RTV on CYP3A4 metabolism. Coadministration of medications that induce or inhibit CYP3A4 may respectively decrease or increase exposures of EVG and COBI. Coadministration of medications that are CYP3A4 substrates may result in clinically significant adverse reactions that are severe, life-threatening, or fatal, or may result in loss of therapeutic effect if dependent on conversion to an active metabolite due to CYP3A4 inhibition by COBI.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir, in the form of tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Genvoya or Stribild. COBI inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL from baseline in adults. Creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, but the actual GFR might be only minimally changed.[3] Significant increases in serum creatinine levels >0.4 mg/dL from baseline may represent renal toxicity and should be evaluated. People who experience a confirmed increase in serum creatinine levels should be closely monitored for renal toxicity; clinicians should monitor creatinine levels for further increases and perform a urinalysis to look for evidence of proteinuria or glycosuria.[4]

Major Toxicities

- *More common:* Nausea, diarrhea, fatigue, headache, flatulence
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and FTC. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children who were taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TAF or TDF,

including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TAF or TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Genvoya or Stribild. This nephrotoxicity may be more pronounced in patients with preexisting renal disease.[4] Although postmarketing cases of renal impairment have been reported with TAF, Genvoya, which contains TAF, has an improved bone and renal safety profile in children and adults when compared to Stribild, which contains TDF.[5,6] However, Genvoya is associated with greater increases in lipid levels than Stribild, according to findings from large-scale clinical trials in adults.

Resistance

The International Antiviral Society–USA maintains a list of updated HIV drug resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. There is phenotypic cross-resistance between EVG and raltegravir (RAL).[7]

Pediatric Use

Approval

Genvoya (EVG/c/FTC/TAF) is approved by the U.S. Food and Drug Administration (FDA) for use in ARV-naive children and adolescents with HIV weighing ≥25 kg. It also can be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

Stribild (EVG/c/FTC/TDF) is approved by the FDA as a complete regimen for use in children and adolescents aged ≥12 years and weighing ≥35 kg. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.[8]

Efficacy

EVG/c/FTC/TDF was found to be non-inferior to efavirenz/emtricitabine/TDF (EFV/FTC/TDF)[9-11] and atazanavir/ritonavir plus FTC/TDF in adults through 144 weeks of treatment.[12-14]

Studies of EVG/c/FTC/TDF and EVG/c/FTC/TAF in children with HIV aged ≥12 years and weighing ≥35 kg have demonstrated 90% efficacy (as measured by virological suppression) similar to that seen in adults through 24 weeks and 48 weeks of study, respectively.[15,16]

EVG/c/FTC/TAF is FDA approved to treat children weighing ≥25 kg based on 24 weeks of data in 23 children.[17] In this study, all children who had been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months were switched from their current regimens to EVG/c/FTC/TAF and all participants maintained virological suppression (HIV-1 RNA <50 copies/mL) at Week 24.

A retrospective analysis of integrase strand transfer inhibitor (INSTI) use in children and adolescents showed that 83.7% (61/73) of patients on an elvitegravir/cobicistat (EVG/c)-containing therapy

continued their prescribed regimen through the end of the study follow-up period (median [interquartile range (IQR)] 2.0 [1.4–2.7] years of exposure). Treatment interruption due to virologic occurred in 4.1% (3/73) of those on EVG/c, which was comparable to that of dolutegravir (DTG)-based regimens (3.7% [5 of 134 participants]) and lower than RAL-based regimens (17.3% [19 of 110 participants]). Two of the participants who experienced virologic failures with EVG had major INSTI drug-resistance mutations, but both attained virologic suppression after switching to regimens containing darunavir (DRV) or DRV with DTG.[18]

In a PK, safety, and efficacy study with a low-dose tablet in children aged ≥2 years and weighing ≥14 kg to <25 kg, children had to be virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months prior to entry.[19] In the most recent analysis, virologic suppression was maintained[20] in 27 (100%) of 27 children at Week 16, 26 (96%) of 27 children at Week 24, and 26 (96%) of 27 children at Week 48. No participant discontinued the study drug because of adverse events or met the criteria for resistance analyses through Week 48. At least 90% of children reported that swallowing the low-dose tablet was "easy" or "super easy" and perceived the tablet size when swallowing as "okay" at baseline, Week 4, and Week 24.[19]

Pharmacokinetics

EVG/c/FTC/TDF (Stribild)

The PK of EVG 150 mg/c 150 mg/FTC 200 mg/TDF 300 mg tablet were evaluated in 14 treatment-naive adolescents with HIV who were between 12 and <18 years of age and weighing ≥35 kg. EVG area under the plasma concentration versus time curve over the dosing interval (AUC_{tau}) and peak concentrations (C_{max}) were 30% higher (90% confidence interval [CI], 105% to 162%) and 42% higher (90% CI, 116% to 173%), respectively, in comparison to historical data in adults. EVG concentrations at the end of the dosing interval (C_{tau}) were 6% higher (90% CI, 70% to 160%) than in adults, and approximately ninefold higher than the protein-adjusted 95% inhibitory concentration ($PA\text{-}IC_{95}$) of 44.5 ng/mL for EVG. COBI, FTC, and TFV exposures were comparable to those measured in adults.[16]

EVG/c/FTC/TAF (Genvoya)

The PK of EVG 150 mg/c 150 mg/FTC 200 mg/TAF 10 mg tablet have been evaluated in adolescents 12 to <18 years of age weighing ≥35 kg and children 6 to <12 years of age weighing ≥25 kg.[17] AUC_{tau}, C_{max}, and C_{tau} for EVG, COBI, FTC, TAF, and TFV were comparable to or higher than those measured in adults with HIV in both cohorts (see Tables A and B below).

The PK of a low-dose FDC tablet containing EVG 90 mg/c 90 mg/FTC 120 mg/TAF 6 mg were evaluated in 27 children with HIV weighing ≥14 kg and <25 kg.[19] EVG and TAF AUC_{tau} were higher in comparison to historical data in adults receiving full-strength Genvoya (see Tables A and B below). EVG C_{tau} was 21% lower (90% CI [53.1% to 117%]) in children versus adults but was approximately 4.4-fold higher and ninefold higher than the $PA\text{-}IC_{95}$ and protein-adjusted 50% inhibitory concentration ($PA\text{-}IC_{50}$) for wild-type virus, respectively. However, EVG C_{tau} measured in this cohort was lower than those previously measured in children and adolescents weighing ≥25 kg on EVG at the 150-mg dose. COBI, FTC, and TFV exposures were all comparable to or higher than historical data in adults.

Table A. Pharmacokinetics of EVG, COBI, FTC, TAF, and TFV (Genvoya) in Children and Adolescents with HIV Between 2 to <18 Years of Age and Weighing ≥14 kg

Component	Parameter	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[19]		Children Aged 6 to <12 Years and Weighing ≥25 kg[17]		Adolescents Aged 12 to <18 Years and Weighing ≥35 kg[15]		Adults[a15,17]	
		n	GLSM	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
EVG	AUC_{tau} (ng·h/mL)	27	29,900	22	33,814 (58%)	24	23,840 (26%)	19	22,800 (35%)
	C_{max} (ng/mL)	27	2,850	23	3,055 (39%)	24	2,230 (19%)	19	2,100 (34%)
	C_{tau} (ng/mL)	27	195	23	370 (119%)	24	301 (81%)	19	290 (62%)
COBI	AUC_{tau} (ng·h/mL)	27	12,300	20	15,891 (52%)	23	8,241 (36%)	19	9,500 (34%)
	C_{max} (ng/mL)	27	1,270	23	2,079 (47%)	24	1,202 (35%)	19	1,500 (28%)
	C_{tau} (ng/mL)	27	16.6	23	96 (169%)	15	25 (180%)	19	20 (85%)
FTC	AUC_{tau} (ng·h/mL)	27	18,600	22	20,629 (19%)	24	14,424 (24%)	19	11,714 (17%)
	C_{max} (ng/mL)	27	2,810	23	3,397 (27%)	24	2,265 (23%)	19	2,056 (20%)
	C_{tau} (ng/mL)	27	77.4	23	115 (24%)	23	102 (39%)	19	95 (47%)
TAF	AUC_{tau} (ng·h/mL)	27	344	23	333 (45%)	24	189 (56%)	539	206 (72%)
	C_{max} (ng/mL)	27	218	23	313 (61%)	24	167 (64%)	539	162 (51%)
TFV	AUC_{tau} (ng·h/mL)	27	327	23	440 (21%)	23	288 (19%)	841	293 (27%)
	C_{max} (ng/mL)	27	19.1	23	26 (21%)	23	18 (24%)	841	15 (26%)
	C_{tau} (ng/mL)	27	11.1	23	15 (25%)	23	10 (21%)	841	11 (29%)
TFV-DP in PBMC	C_{0h} (fmol/10^6 cells)	—	—	—	—	12	222 (94%)	21	121 (91%)

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from a Phase 2 study GS 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 GS studies 104 and 111.

Key: AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{0h} = concentration at time 0 (pre-dose); C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; EVG = elvitegravir; fmol = femtomole; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; ng = nanogram; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir-diphosphate

Table B. Comparisons of EVG, COBI, FTC, TAF, and TFV (Genvoya) Pharmacokinetics in Children and Adolescents with HIV Between 2 and <18 Years of Age and Weighing ≥14 kg to Adult Values

Component	Parameter	% GLSM (90% CI) Compared with Adult Values[a]			
		Dose (mg)	Children **Aged ≥2 Years and Weighing ≥14 to <25 kg**[17]	Dose (mg)	Children Aged 6 to **<12 Years and Weighing ≥25 kg**[19]
EVG	AUC_{tau} (ng·h/mL)	90	139 (112,172)	150	134 (104,173)
	C_{max} (ng/mL)		143 (113,180)		141 (115,173)
	C_{tau} (ng/mL)		79 (53,117)		86 (55,133)
COBI	AUC_{tau} (ng·h/mL)	90	—	150	158 (126,198)
	C_{max} (ng/mL)		—		127 (98,165)
	C_{tau} (ng/mL)		—		171 (95,310)
FTC	AUC_{tau} (ng·h/mL)	120	—	200	175 (160,192)
	C_{max} (ng/mL)		—		164 (145,184)
	C_{tau} (ng/mL)		—		125 (107,146)
TAF	AUC_{tau} (ng·h/mL)	6	193 (166,224)	10	171 (147,199)
	C_{max} (ng/mL)		150 (116,195)		182 (146,225)
TFV	AUC_{tau} (ng·h/mL)		—		152 (142,163)
	C_{max} (ng/mL)		—		173 (161,186)
	C_{tau} (ng/mL)		—		143 (132,155)

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

Key: AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{max} = maximum observed plasma concentration of drug; COBI = cobicistat; C_{tau} = observed drug concentration at the end of the dosing interval; CI = confidence interval; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; mg = milligram; ng = nanogram; TAF = tenofovir alafenamide; TFV = tenofovir

Coadministration of Elvitegravir, Cobicistat, and Darunavir

The combination of Stribild or Genvoya plus DRV may provide a low-pill-burden regimen for treatment-experienced individuals. However, an unfavorable drug interaction between EVG/c and DRV is possible, and the available data on the significance of the interaction and efficacy are conflicting.[21-24] The most rigorous drug interaction study in HIV-seronegative adults found 21% lower DRV trough concentrations (C_{trough}) and 52% lower EVG C_{trough} in combination with DRV 800 mg plus EVG/c 150 mg/150 mg once daily compared to the administration of either DRV/c 800 mg/150 mg once daily or EVG/c 150 mg/150 mg once daily alone.[25] Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults who were on five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus DRV 800 mg once daily.[23] Given

the uncertainty around the true magnitude of the drug interaction and the absence of pediatric data, viral load should be closely monitored in children taking this combination.

Toxicity

In studies comparing EVG/c/FTC/TDF or EVG/c/FTC/TAF over 48 weeks in 1,733 adults, those receiving EVG/c/FTC/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; $P < 0.0001$), significantly less proteinuria (median percent change in protein −3% vs. +20%; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean percent change −1.30% vs. −2.86%; $P < 0.0001$) and hip (−0.66% vs. −2.95%; $P < 0.0001$).[6] Larger increases in fasting lipid levels were observed with EVG/c/FTC/TAF than with EVG/c/FTC/TDF; the median increases in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were all higher in patients who received EVG/c/FTC/TAF.

In children and adolescents, EVG/c/FTC/TAF is generally preferred over EVG/c/FTC/TDF because of the lower risk of renal and bone toxicity with EVG/c/FTC/TAF compared to EVG/c/FTC/TDF (see the Tenofovir Alafenamide section). Long-term bone safety data through 96 weeks with EVG/c/FTC/TAF in adolescents weighing ≥35 kg revealed no concerns for toxicity[26] in this age group on the basis of BMD (median change from baseline spine BMD height-age [HA] z-score +0.14 and total body less head [TBLH] HA z-score of −0.07) and serum biomarkers of bone formation and resorption.[27]

In the approval study of EVG/c/FTC/TAF in children weighing ≥25 kg, no study discontinuations occurred due to medication toxicity. Long-term bone safety data with EVG/c/FTC/TAF through 96 weeks revealed no concerns for toxicity in this cohort on the basis of BMD (median change from baseline spine BMD HA z-score of −0.2 and TBLH HA z-score of −0.32) and serum biomarkers of bone formation and resorption.[20] A concerning decline in CD4 T lymphocyte (CD4) cell counts was observed in all 23 children over the first 24 weeks of EVG/c/FTC/TAF treatment.[17] CD4 counts declined by a median of 130 cells/mm^3 (with a range of −472 cells/mm^3 to 266 cells/mm^3) from baseline. However, after enrolling additional children (for a total of 52 participants),[28] the median CD4 count decline at 48 weeks was 25 cells/mm^3 and at 96 weeks was 45 cells/mm^3. Additionally, the CD4 percentage did not significantly change across Weeks 24, 48, and 96.[20] The mechanism for the reduction in CD4 count is unclear, and this reduction has only been reported in this study. Plasma exposures of all four drugs were higher in these children than the plasma exposures seen in historical data from adults, but no association was identified between plasma exposures of the four components of EVG/c/FTC/TAF and CD4 counts.[29]

In an ongoing PK, safety, and efficacy study with a low-dose EVG/c/FTC/TAF tablet in children aged ≥2 years and weighing ≥14 kg to <25 kg,[19] long-term bone safety data with the low-dose formulation through 48 weeks revealed no concerns for bone safety in this cohort on the basis of BMD (median change from baseline in spine BMD HA z-score +0.14 and TBLH HA z-score of −0.06) and serum biomarkers of bone formation and resorption.[27] CD4 counts decreased[20] by a mean of 187 cells/mm^3 between baseline and Week 48, although the CD4 percentage did not differ (mean [standard deviation] change of 0.0 [<5.0]). In a cumulative analysis of two pediatric cohorts (Cohort 2 aged 6 to <12 years and weighing ≥25 kg and Cohort 3 aged ≥2 years and weighing ≥14 kg to <25 kg) on EVG/c/FTC/TAF once daily for at least 48 weeks, the absolute lymphocyte counts and absolute CD4 counts decreased from baseline to Week 48 in both cohorts, with larger decreases in the younger cohort.[30] Median (IQR) absolute lymphocyte counts (×10^3 per µL) at baseline in Cohort 2

and Cohort 3 were 2.31 (range, 1.92–2.78) and 2.96 (range, 2.39–3.82), respectively. The absolute lymphocyte counts decreased during treatment (particularly in Cohort 3), with changes of −0.04 (range, −0.67 to 0.29) and −0.52 (range, −1.16 to 0.05) in Cohorts 2 and 3, respectively, at Week 48. Small decreases were seen in median (IQR) absolute CD4 counts (cells/µL), with changes of −33 (−194 to 80) and −187 (−370 to 44) in Cohorts 2 and 3, respectively, at Week 48. However, the relative proportion of CD4 cells and the CD4:CD8 ratio remained stable during treatment. Overall, the decline in absolute CD4 counts mirrored known physiological fluctuations in young children and was mainly observed in those aged <6 years.[30]

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